Familial persistent developmental stuttering: genetic perspectives

Gagueira desenvolvimental persistente familial: perspectivas genéticas

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ABSTRACT

Stuttering is a disorder of oral communication that has a multidimensional character. The biological predisposition in the development of stuttering is still not well understood, but genetic contributions to this predisposition are enhanced by both references to the familial aggregation of stuttering and to familial stammering, which have appeared in the literature for over 70 years. Thus, we conducted a review as to the likely genetic factors involved in the manifestation of familial persistent developmental stuttering. The identification of genes related to stuttering, as well as alterations in their structures (e.g., mutations), contribute significantly to its understanding. The exact transmission pattern of genetic inheritance for stuttering is still not clearly defined and might probably be different among different families and populations. Genomic analysis have shown, concomitantly, the relevance of the genetic components involved and their complexity, thus suggesting that this is a polygenic disease in which several genes of different effects may be involved with the increased susceptibility of occurrence of stuttering. The clinician should be alert to the fact that a child with positive familial history for stuttering may have a strong tendency to develop the disorder chronically. It is important that the clinician is aware, in order to provide precise information about the disorder to the families. Objective evaluations and controlled treatments play an important role in the knowledge of the disorder's development.

Keywords: Speech, language, and hearing sciences; Speech; Stuttering/etiology; Genetics; Genes; Inheritance patterns

INTRODUCTION

Speech involves linguistic (formal, segmental aspects) and paralinguistic (prosodic aspects, suprasegmental) components, processed by different neural ways, which, integrated and in sync, are basic for the constitution of one's fluent speech that must have a continuous flow, maintaining sequence, speed, rhythm, and duration considered normal so that phonological, lexical, morphologic and/or syntactic units are adequately produced. Involuntary breaks or ruptures in any linguistic units characterize the disfluencies which can be considered common (hesitations; interjections; revisions; unfinished words; and repetition of words, segments or phrases) or stuttering (repetition of sounds or syllables; prolongations; blockades; pauses and intrusion). Stuttering is a complex disorder of the verbal communication, that cannot be considered as a single nosologic entity, as it has a multidimensional characteristic, and is often experienced by the individual as a loss of control of their own speech[1].

During infancy, due to the complex process of language acquisition and development, it is common for children to present disfluencies (hesitations, repetition of sounds, syllables or words), tending to stabilize the speech flow after acquiring greater linguistic-phonologic and morphosyntactic-semantic-pragmatic domain. In 80% of the children these disfluencies are normal and tend to disappear in six months. However, in children who present predisponent factors for stuttering, these disfluencies will

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be able to evolve into a chronic state known as developmental stuttering, which affects 5% of the children, mainly in the age group between 18 months and 7 years, taking place until 12 years of age in some cases, average prevalence of 1% in the population. Amongst the risk factors for the developmental stuttering described in the literature, age gender; duration of the disfluencies, type of ruptures, pre, peri and post natal morbidity, associated communication deficits; psychosocial stresses; positive family history for stuttering; and reaction from the child, the family and the society with respect to the problem[1].

Stuttering can also occur in additional two distinct circumstances, from injuries, in an ample range of cerebral areas, which is called acquired or neurogenic stuttering[2] and another one, involving psychological aspects.

Developmental stuttering is subdivided in: persistent developmental – present during a period equal or greater than 36 months after its manifestation; late recovery – recovered between 18 and 36 months after its onset; and early recovery – recovery before 18 months after the instauration of the disorder[3]. In cases where there is recurrence in the family where two or more individuals are affected by stuttering, this is called familial developmental[4], purpose of this work. In cases where there is only one stutterer in the family, it is called isolated developmental. Thus, the classification of stuttering[1-4] can be schematically represented (Figure 1).

The biological predisposition in the development of stuttering is not yet well understood, but genetic contributions for this predisposition are strengthened by references in regard to the familial aggregation of the stuttering, that have appeared in literature for more than 70 years[5-8]. Thus, due to the excellent and recent scientific findings in the biological scope, we look to establish a revision in regard to the probable genetic factors involved with the manifestation of the persistent developmental familial stuttering and in such a way to contribute with a better understanding.

LITERATURE REVIEW

The main arguments that base the involvement of genetic factors on stuttering are: studies of twins, with bigger agreement between monozygotic twins (62.5% to 90%) in relation to dizygotic twins (6.6% to 9%)[8-13]; familial aggregation, where the disfluencies are more inclined to develop in consanguineous individuals, in detriment to the cases where such relation does not occur[9,14-16] and the phenotypical similarity developed among stutterers, such as repetitions, prolongations of sounds and syllables of words without being connected to differences of language and culture[15,17-19].

Thus, it is believed that there are regions of the genome that carry important information to the human development (genes), which once modified (mutated), can promote small and subtle changes in the structure and function of the brain[20-23], in individuals with familial persistent developmental stuttering , which has led research groups to carry through ample genetic studies in the last few decades.

The familial persistent developmental stuttering is considered a disease with standard of complex or multifactorial inheritance[24]. Such characteristic is a result of complex interactions of several predisponent factors such as genotype in one or more loci and diverse environmental components capable of activating, speeding up or intensifying the manifestation of the illness. Studies of genetic mapping, associated with varied and complex statistical analyses, such as studies of association and analysis link, have been extensively used in the processes of localization and identification of loci and alleles specifically involved that supply a definitive proof of the genetic contribution to stuttering[25].

The search for genes that influence complex characteristics has been much more challenging than the genetic studies of Mendelian traces[26]. Some factors contribute to this problem, including etiological and genetic heterogeneity and the neces-

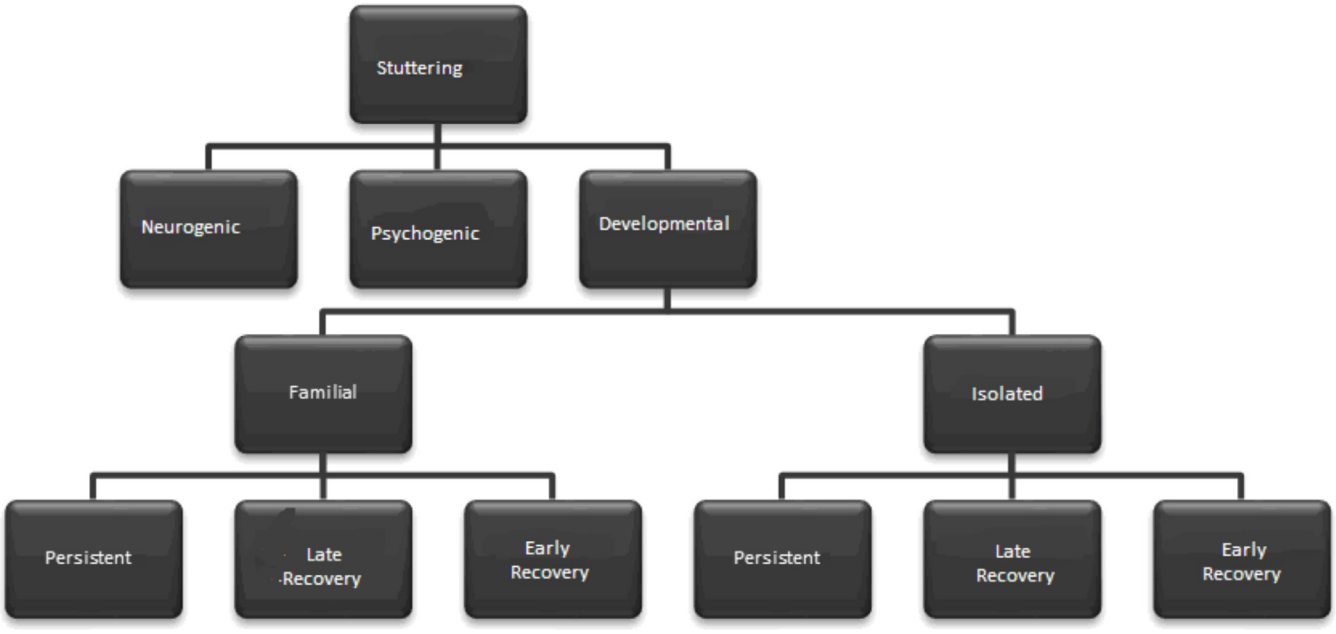

Figure 1. Stuttering classification

sity of complex genetic models with several variables for the purpose of locus, interactions gene-gene and gene-environment, what justifies the use of several statistical methods. An adequate method of genetic analysis for stuttering demands a combination of steps for the identification of chromosomal regions, in which the genetic variations inhabit and that characterize the complex etiology of this illness[25]

The accurate model of transmission of the genetic inheritance in stuttering has not been well defined yet and, moreover, there is the possibility of it being different among the different populations[27]. There are indications that a main gene exists, responsible for the increase of the risk of occurrence of stuttering, when combined with other genes[28]. Several genetic studies were carried through with the objective to identify possible regions and/or genes related with the disease (Table 1).

Recent discoveries have pointed to several regions of the genome that once modified can possibly be related to stuttering as for example, genes from receiver family (DRD2; DRD3) and dopamine transporters (SLC6A3)[29,30] as well as others until recently related to other illnesses, as the Mucopolysaccharidosis Type II and III - GNPTAB (N-acetylglucosamine-1--phosphate transferase, alpha and beta subunits)[31] GNPTG

Table 1. General overview of the genetic studies published

Chromosomal region	Method	Sample group of disfluencies	Reference
1	Linkage analysis NPL = 1.1	Hutterites *n	Cox N, Yairi E. Genetics of stuttering: insights and recent advances. ASHA leader 5 (16). Bethesda: Amer. Speech Lang. Hear. Association. Abstract. 2000(674).
1	Genomic selection (linkage analysis)	Pakistanis n=56 families	Riaz N, Steinberg S, Ahmad J, Pluzhnikov A, Riazuddin S, Cox NJ, et al. Genomewide significant linkage to stuttering on chromosome 12. Am J Hum Genet. 2005;76(4):647-51.
3q	Genomic selection (linkage analysis) and study of dopamine D3 receptor gene (DRD3)	Pakistanis n=1 family	Raza, Riazuddin, Drayna[30]
5	Genomic selection (linkage analysis)	Pakistanis n=56 families	Riaz N, Steinberg S, Ahmad J, Pluzhnikov A, Riazuddin S, Cox NJ, et al. Genomewide significant linkage to stuttering on chromosome 12. Am J Hum Genet. 2005;76(4):647-51.
5	Study of the gene candidate dopamine transporter DAT (SLC6A3) gene	Chinese Population *Han* n=112 individuals	Lan et al.[29]
7	Genomic selection (linkage analysis)	Pakistanis n=56 families	Riaz N, Steinberg S, Ahmad J, Pluzhnikov A, Riazuddin S, Cox NJ, et al. Genomewide significant linkage to stuttering on chromosome 12. Am J Hum Genet. 2005;76(4):647-51.
7	Genomic selection (linkage analysis) (group of men) LOD = 2.99 - 153cM	Americans (European origin), Swedish and Israelis n=100 families	Suresh R, Ambrose N, Roe C, Pluzhnikov A, Wittke-Thompson JK, Ng MC et al. New complexities in the genetics of stuttering: significant sex-specific linkage signals. Am J Hum Genet. 2006;78(4):554-63.
7q	Analysis of gene CNTNAP2	Brazilian patient	Petrin et al.[35]
9	Genomic selection (linkage analysis) (recovered and persistent stutterers) LOD = 2.3 - 60cM	Americans (European origin), Swedish and Israelis n=100 families	Suresh R, Ambrose N, Roe C, Pluzhnikov A, Wittke-Thompson JK, Ng MC et al. New complexities in the genetics of stuttering: significant sex-specific linkage signals. Am J Hum Genet. 2006;78(4):554-63.
11	Study of the gene candidate dopamine D3 receptor gene (DRD3)	Chinese Population *Han* n=112 individuals	Lan et al.[29]
12q	Genomic selection (linkage analysis)	Pakistanis n=56 families	Riaz N, Steinberg S, Ahmad J, Pluzhnikov A, Riazuddin S, Cox NJ, et al. Genomewide significant linkage to stuttering on chromosome 12. Am J Hum Genet. 2005;76(4):647-51.
12q	Analysis of genes GNPTAB/GNPTG/ NAGPA	Pakistanis n=46 individuals	Kang et al.[32]

Quadro 1. continuação

Chromosomal region	Method	Sample group of disfluencies	Reference
13	Genomic selection (linkage analysis) NPL = 1.38	Hutterites *n	Cox N, Yairi E. Genetics of stuttering: insights and recent advances. ASHA leader 5 (16). Bethesda: Amer Speech Lang Hear Association. Abstract. 2000 (674).
15	Genomic selection (linkage analysis) (recovered and persistent stutterers) LOD = 1.95 - 23cM	Americans (European origin), Swedish and Israelis n=100	Suresh R, Ambrose N, Roe C, Pluzhnikov A, Wittke-Thompson JK, Ng MC et al. New complexities in the genetics of stuttering: significant sex-specific linkage signals. Am J Hum Genet. 2006;78(4):554-63.
16q	Genomic selection (linkage analysis)	1 Pakistani family of consanguineous marriages n=26 individuals (14 affected)	Raza et al.[16]

Note: *n = number of individuals in the study not available

(N-acetylglucosamine-1-phosphate transferase, gammasubunit), and to gene NAGPA (N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase) that acts in the same metabolic way[32]. In the chromosomic regions 7q31 and 7q35 genes FOXP2 (Forkhead Box P2) and CNTNAP2 (2 Contactin-associated protein-like) are located which have been, permanently, pointed as genes directly related to speech and language disorders[33,34].

Evidences of interruptions that affect correct functionalities of the genes, such as alterations presented in the variation of the number of copies in certain regions of the genome (CNVs), in the chromosomic rearrangements and mutations, can imply in a variety of genetic and, consequently, neuropathological conditions[35]. Thus, it is believed that these alterations must intervene with the whole dynamics of the neuronal development and that disturbances in this direction result in a significant increase of the possibilities of some form of neurological dysfunction with probable implications in relation to the nervous centers of speech and language[36], which once modified, must promote the occurrence of disfluencies that can culminate into the development of the stuttering.

The genetic predisposition can affect the fluency in regard to the capacity of the individual in relation to the motor control of their own speech. An inefficient response to the muscular effort and its independent response can imply in muscular contractions in different times or the passages with desynchronized acts[37]. Recent evidences suggest that persistent familial developmental stuttering occurs due to cerebral dysfunctions[38], attributed directly to genetic factors[20,39,40].

DISCUSSION

It becomes evident that the genes that predispose stuttering, until then listed, are being better studied and that alterations in one or more genes can contribute significantly for the manifestation of stuttering. Moreover, an accurate model of transmission is not yet clearly defined and can probably be different among different families and populations[27].

Since this is a complex illness of multidimensional character and inheritance, stuttering must be investigated taking into consideration all the risk factors, for the attainment of a precise and definite diagnosis and of the patients who have it. The results obtained from genomic analyses, by means of linkage and association studies, in the identification of possible candidate genes, as well as of alterations and interactions in cellular pathways that can be connected to the phenotype, demonstrate, concomitantly, the relevance of the involved biological components and its complexity, what suggests in fact, to be about a polygenic illness in which diverse genes, of varied effects, can be involved with the increase of the susceptibility of occurrence of stuttering[25].

FINAL CONSIDERATIONS

The overlapping of several genetic factors possibly involved with the characterized manifestation of stuttering and those already characterized to the speech and language disorders such as Tourette syndrome, autism, the specific language disorder and dyslexia, allow inferring that there probably is a sharing of the involved basic molecular mechanisms, which once supplemented from the performance of other biological factors (secondary genes) and environmental can imply in stuttering.

Identifying the genetic variation responsible for stuttering is a great challenge faced by several research groups which, once better understood is determinant for the understanding of its primary etiology, of epidemiologic aspects and the possible involved not-genetic factors and that has important implications in the patient's diagnosis and the prognostic.

Thus, the speech therapist will have to be alert to the fact that a child with positive familial history for stuttering will have a strong tendency to develop the disorder in a chronic way, in addition to possibly presenting other relatives affected in the family. It is important that the physician is apt to provide the families with necessary guidance about the disorder. The objective evaluations and the controlled treatments have a very important role in controlling the evolution of the disorder.

RESUMO

A gagueira é uma desordem da comunicação oral que tem uma característica multidimensional. A predisposição biológica no desenvolvimento da gagueira ainda não é bem compreendida, mas contribuições genéticas para esta predisposição são reforçadas tanto por referências à agregação familial da gagueira, quanto à gagueira familial, que têm aparecido na literatura há mais de 70 anos. Assim, procuramos estabelecer uma revisão quanto aos prováveis fatores genéticos envolvidos com a manifestação da gagueira desenvolvimental persistente familial. A identificação de genes relacionados à gagueira, bem como de alterações em suas estruturas (por exemplo, mutações), contribuem significativamente para sua compreensão. O modelo exato de transmissão da herança genética para a gagueira ainda não está claramente definida e, provavelmente pode ser diferente entre diferentes famílias e populações. As análises genômicas demonstram, concomitantemente, a relevância dos componentes genéticos envolvidos e sua complexidade, sugerindo assim tratar-se de uma doença poligênica, na qual diversos genes de efeitos variados podem estar envolvidos com o aumento da susceptibilidade de ocorrência da gagueira. O clínico deverá estar alerta ao fato de que uma criança com histórico familial positivo para gagueira poderá ter uma forte tendência a desenvolver o distúrbio de forma crônica. É importante que o clínico esteja atento, de modo a fornecer às famílias orientações precisas sobre o distúrbio. As avaliações objetivas e os tratamentos controlados têm um papel muito importante para o domínio da evolução do distúrbio.

Descritores: Fonoaudiologia; Fala; Gagueira/etiologia; Genética; Genes; Padrões de herança

REFERENCES

1. Andrade CR de. Abordagem neurolinguística e motora da gagueira. In: Tratado de Fonoaudiologia. Org. Ferreira LP, Befi-Lopes DM; Limongi SCO. Ed Roca: São Paulo; 2004. p. 1001-26.
2. Grant AC, Biousse V, Cook AA, Newman NJ. Stroke-Associated Stuttering. Arch Neurol. 1999;56(5):624-27.
3. Yairi E, Ambrose NG, Cox N. Genetics of stuttering: A critical review. J Speech Hear Res. 1996;39(4):771-84.
4. Yairi E, Ambrose NG, Paden EP, Throneburg RN. Predictive factors of persistence and recovery: pathways of childhood stuttering. J Commun Disord. 1996;29(1):51-77.
5. Bryngleson B. Sidedness as an etiological factor in stuttering. The Pedagogical Seminary and Journal of Genetic Psychology. 1935;47(1):204-17.
6. Wepman JM. Familial Incidence in stammering. J Speech Disord. 1939;4(3):199-204.
7. Gray M. The X Family: a clinical and laboratory study of a "stuttering" family. J Speech Disord. 1940;5(4):343-8.
8. Howie PM. Concordance for stuttering in monozygotic and dizygotic twin pairs. J Speech Hear Res.1981;24(3):317-21.
9. Felsenfeld S, Kirk KM, Zhu G, Statham DJ, Neale MC, Martin NG. A study of the genetic and environmental etiology of stuttering in a selected twin sample. Behav Genet. 2000;30(5):359-66.
10. Ooki S. Genetic and environmental influences on stuttering and tics in Japanese twin children. Twin Res Hum Genet. 2005;8(1):69-75.
11. Dworzynski K, Remington A, Rijsdijk F, Howell P, Plomin R. Genetic etiology in cases of recovered and persistent stuttering in an unselected, longitudinal sample of young twins. Am J Speech Lang Pathol. 2007;16(2): 169-78.
12. Fagnani C, Fibiger S, Skythe A, Hjelmborg JV. Heritability and environmental effects for self-reported periods with stuttering: a twin study from Denmark. Logoped Phoniatr Vocol. 2011;36(3):114-20.
13. Rautakoski P. Genetic and environmental effects on stuttering: a twin study from Finland. J Fluency Disord. 2012;37(3):202-10.
14. Andrews G, Morrisyates A, Howie P, Martin NG. Genetic factors in stuttering confirmed. Arch Gen Psychiatry. 1991;48(11):1034-5.
15. Felsenfeld S, Plomin R. Epidemiological and offspring analyses of developmental speech disorders using data from the Colorado Adoption Project. J Speech Lang Hear Res.1997;40(4):778-91.
16. Raza MH, Amjad R, Riazuddin S, Drayna D. Studies in a consanguineous family reveal a novel locus for stuttering on chromosome 16q. Hum Genet. 2012;131(2):311-13.
17. Wingate ME. A standard definition of stuttering. J Speech Hear Disord. 1964;29:484-9.
18. Bloodstein O, Grossman M. Early stutterings: some aspects of their form and distribution. J Speech Hear Res. 1981;24(2):298-302.
19. Bloodstein O. A handbook on stuttering. 5a ed. Chicago: National Easter Seal Society; 1995.
20. Yairi E, Ambrose N. Onset of stuttering in preschool children: selected factors. J Speech Hear Res. 1992;35(4):782-8.
21. Ambrose NG, Yairi E. Normative disfluency data for early childhood stuttering. J Speech Lang Hear Res. 1999;42(4):895-909.
22. Fox PT, Ingham RJ, Ingham JC, Zamarripa F, Xiong JH, Lancaster JL. Brain correlates of stuttering and syllable production: A PET performance-correlation analysis. Brain. 2000;123(10):1985-2004.
23. Foundas AL, Corey DM, Angeles V, Bollich AM, Crabtree–Hartman E, Heilman KM. Atypical cerebral laterality in adults with persistent developmental stuttering. Neurology. 2003;61(10):1378-85.
24. Ambrose NG, Cox NJ, Yairi E. The genetic basis of persistence and recovery in stuttering. J Speech Lang Hear Res. 1997;40(3):567-80.
25. Wittke-Thompson JK, Ambrose N, Yairi E, Roe C, Cook EH, Ober C, et al. Genetic studies of stuttering in a founder population. J Fluency Disord. 2007;32(1):33-50.
26. Botstein D, Risch N. Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet. 2003;33(Suppl):228-37.
27. Alm PA, Risberg J. Stuttering in adults: the acoustic startle response, temperamental traits, and biological factors. J Commun Disord. 2007;40(1):1-41.
28. Yairi E, Ambrose NG, Grinager N. Early childhood stuttering. Austin: Pro-Ed, Inc; 2005.
29. Lan J, Song M, Pan C, Zhuang G, Wang Y, Ma W, et al. Association between dopaminergic genes (SLC6A3 and DRD2) and stuttering among Han Chinese. J Hum Genet. 2009;54(8):457-60.
30. Raza MH, Riazuddin S, Drayna D. Identification of an autosomal recessive stuttering locus on chromosome 3q13.2-3q13.33. Hum Genet. 2010;128(4):461-3.
31. Fedyna A, Drayna D, Kang C. Characterization of a mutation commonly associated with persistent stuttering: evidence for a founder mutation. J Hum Genet. 2011;56(1):80-2.
32. Kang C, Riazuddin S, Mundorff J, Krasnewich D, Friedman P, Mullikin JC, et al. Mutations in the lysosomal enzyme-targeting pathway and persistent stuttering. N Engl J Med. 2010;362(8):677-85.

33. Peter B. Replication of CNTNAP2 association with nonword repetition and support for FOXP2 association with timed reading and motor activities in a dyslexia family sample. J Neurodev Disord. 2011;3(1):39-49.
34. Fujita E, Tanabe Y, Momoi MY, Momoi T. CNTNAP2 expression in the cerebellum of Foxp2 (R552H) mice, with a mutation related to speech-language disorder. Neurosci Lett. 2012;506(2):277-80.
35. Petrin AL, Giacheti CM, Maximino LP, Abramides DV, Zanchetta S, Rossi NF, et al. Identification of a microdeletion at the 7q33-q35 disrupting the CNTNAP2 gene in a Brazilian stuttering case. Am J Med Genet. 2010;152A(12):3164-72.
36. Newbury D, Fisher S, Monaco A. Recent advances in the genetics of language impairment. Genome Med. 2010;2(1):6.
37. Andrade CR. História natural da gagueira – estudo I: perfil da fluência. Pró-Fono. 2002;14(3):351-60.
38. Sommer M, Koch MA, Paulus W, Weiller C, Büchel C. Disconnection of speech-relevant brain areas in persistent developmental stuttering. Lancet. 2002;360(9330):380-3.
39. Foundas AL, Bollich AM, Corey DM, Hurley M, Heilman KM. Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. Neurology. 2001;57(2):207-15.
40. Ingham RJ, Ingham JC, Finn P, Fox PT. Towards a functional neural systems model of developmental stuttering. J Fluency Disord. 2003;28(4):297-317; quiz 317-8.